DELETION OF INVENTORS

Please correct the inventorship under 37 CFR §1.48(b) by removing the following inventors from the present application:

Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe.

Applicants request that these inventors be deleted, as their inventions are no longer being claimed in the present application as a result of prosecution.

REMARKS

Applicants have cancelled Claim 6 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claim 1 to remove reference to the Figure and to recite that the claimed antibody specifically binds to the polypeptide having the amino acid sequence of SEQ ID NO: 82. Support for this amendment can be found at paragraph [0247] of the specification. Claims 1-5 are presented for examination. Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed January 13, 2005. For the reasons set forth below, Applicants respectfully traverse.

Correction of Inventorship under 37 CFR §1.48(b)

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

Priority Determination:

As an initial matter, the PTO issued the instant Office Action assuming that the earliest priority is the instant filing date, May 3, 2002. The PTO argued that the instant application and priority application Serial No. 10/006,867 do not meet the requirements of 35 U.S.C. § 112, first paragraph. However, for the reasons set forth below, the instant application and the priority application do meet the requirements of 35 U.S.C. § 112, first paragraph, and therefore, are entitled to an earlier priority date.

Applicants have previously listed the priority information for the instant application in a Preliminary Amendment mailed September 3, 2002. The preliminary amendment states that the instant "application is a continuation of, and claims priority under 35 U.S.C. § 120 to, US Application 10/006867 filed 12/6/2001, which is a continuation of, and claims priority under 35 U.S.C. § 120 to, PCT Application PCT/US00/23328 filed 8/24/2000, which is a continuation-in-part of, and claims priority under 35 U.S.C. § 120 to, US Application 09/403297 filed 10/18/1999, now abandoned, which is the National Stage filed under 35 U.S.C. § 371 of PCT

Application PCT/US99/20111 filed 9/1/1999, which claims priority under 35 U.S.C. § 119 to U.S. Provisional Application 60/105881 filed 10/27/1998."

The sequences of SEQ ID NOs: 81 and 82 were first disclosed in U.S. Provisional Application 60/105,881 filed 10/27/1998 as SEQ ID NO:1 and 2 and in Figures 1 and 2. These same sequences were disclosed in PCT/US99/20111 and in 09/403,297 as SEQ ID NO:141 and 142, Figures 85 and 86. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed antibodies, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Thus, Applicants maintain that the present application is fully entitled to the benefit of at least the priority date of August 24, 2000.

Rejection under 35 U.S.C. §101 – Utility

The PTO has rejected Claims 1-6 as lacking a specific, substantial, and credible utility. The PTO argues that utilities asserted in the specification are not specific and substantial or well established. According to the PTO, the claimed antibodies do not have utility "[b]ecause neither the physiological nor the clinical significance of the polypeptide is known, and because the prior art does not support a very close structural relationship to a well described family of known proteins." Office Action at 2. The PTO further states that use of an antibody "is not a specific or substantial use if it is not known what the isolated or expressed protein does or what the specific disease can by [sic] diagnosed with it." *Id.*

The PTO cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) to support its assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue.

One of the asserted utilities for the claimed antibodies is use as a diagnostic tool, as well as therapeutically, based on the data that PRO1557 cDNA is more highly expressed in esophageal tumor and kidney tumor as compared to normal esophagus and normal kidney tissue, respectively. The PTO recognizes this as a "possible utility," however, the PTO asserts that there is no guidance on how to use this information, that no levels are disclosed, that the information is too sparse to allow the encoding polynucleotide to be used as a diagnostic marker for esophageal or kidney tumor, and that even if the polynucleotide had utility, the encoded polypeptide has no such utility because there is no reason to suspect that there is an alteration of polypeptide

sequence or amount in esophageal or kidney tumor versus normal tissue. Office Action, at 3. For the above reasons, the PTO asserts that there is no substantial and specific utility for the claimed antibodies.

Applicants respectfully disagree and submit that for the reasons stated below, the claimed antibodies have a credible, substantial, and specific utility.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d

1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove

that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

The Court in *Fujikawa* relied in part on its decision in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985). In *Cross*, the Appellant argued that basic *in vitro* tests conducted in cellular fractions did not establish a practical utility for the claimed compounds. Appellant argued that more sophisticated *in vitro* tests using intact cells, or *in vivo* tests, were necessary to establish a practical utility. The Court in *Cross* rejected this argument, instead favoring the argument of the Appellee:

> [*I*]*n vitro* results...are generally predictive of *in vivo* test results, i.e., there is a **reasonable correlation** therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. [Appellee] has not urged, and rightly so, that there is an invariable exact correlation between *in vitro* test results and *in vivo* test results. Rather, [Appellee's] position is that successful *in vitro* testing for a particular pharmacological activity establishes a **significant probability** that *in vivo* testing for this particular pharmacological activity will be successful. *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (emphasis added).

The *Cross* case is very similar to the present case. Like *in vitro* testing in the pharmaceutical industry, those of skill in the field of biotechnology rely on the reasonable correlation that exists between gene expression and protein expression (see below). Were there no reasonable correlation between the two, the techniques that measure gene levels such as microarray analysis, differential display, and quantitative PCR would not be so widely used by those in the art. As in *Cross*, Applicants here do not argue that there is "an invariable exact correlation" between gene expression and protein expression. Instead, Applicants' position detailed below is that a measured change in gene expression in cancer cells establishes a "significant probability" that the expression of the encoded polypeptide in cancer will also be changed based on "a reasonable correlation therebetween."

Taken together, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly esophageal and kidney cancer. Applicants are not asserting that the claimed antibodies necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO1557 polypeptide is more highly expressed in esophageal tumor tissue and kidney tumor tissue compared to normal esophageal tissue and normal kidney tumor, respectively;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding change in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the level of mRNA for the PRO1557 polypeptide is increased in esophageal tumor and kidney tumor, compared to normal esophageal tissue and normal kidney tissue, it is likely that the PRO1557 polypeptide is differentially expressed in esophageal tumor and kidney tumor and therefore antibodies to the PRO1557 polypeptide are useful as a diagnostic tool to distinguish tumor from normal tissue.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO has challenged the reliability of the evidence reported in Example 18, and states that it does not provide the expression levels, and that the information is too sparse to allow the encoding polynucleotide to be used as a diagnostic marker for tumors;

2. The PTO cites Hu *et al.* for the assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels;

3 The PTO asserts that even if the polynucleotide had utility, the encoded polypeptide has no such utility because there is no reason to suspect that there is an alteration of polypeptide sequence or amount in esophageal or kidney tumor versus normal tissue. The PTO states that it is not known what the protein does or if the level of the protein in esophageal or kidney tumors corresponds to nucleic acid transcript level. The PTO states that an antibody to a protein has no utility if it is not known what the protein does or what disease can be diagnosed.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). First, Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, (attached as Exhibit 1) which establishes the reliability of the data of Example 18. Second, the reference provided by the PTO not contrary to Applicants' arguments and evidence, and therefore is not evidence to support the PTO's position. Third, Applicants submit that given the well-established correlation between a

change in the level of mRNA with a corresponding change in the levels of the encoded protein, the PRO1557 protein is likely differentially expressed in certain tumors. This provides utility for antibodies to the PRO1557 proteins as cancer diagnostic tools. Fourth, Applicants do not rely on the function of the encoded polypeptides for utility for the claimed antibodies.

Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute or statistical certainty.**

Applicants have established that the Gene Encoding the PRO1557 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1557 polypeptide in certain tumors compared to their normal counterparts is insufficient because the specification provides no information regarding values of the differences in transcript levels, and the disclosure of the specification is too sparse. Applicants also address the PTO's argument that the data do not establish a utility because the specification does not disclose any information on the level of expression, activity, or role of the PRO1557 polypeptide in cancer. Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed antibodies.

Applicants submit herewith a copy of a declaration of J. Christopher Grimaldi, an expert in the field of cancer biology, originally submitted in a related co-pending and co-owned patent application Serial No. 10/063,557 (attached as Exhibit 1). In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples.

He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the PTO's assertions, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (Paragraph 7). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor."

Applicants submit that a lack of known role for PRO1557 in cancer does not prevent its use as a diagnostic tool for cancer. Whether the differential expression of PRO1557 is a cause or result of the esophageal and kidney tumors is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1557 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.) In addition, while Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO has issued several patents claiming differentially expressed polypeptides and antibodies thereto. (*See, e.g.,* U.S. Patent No. 6,414,117 and U.S. Patent No. 6,124,433, attached hereto as Exhibits 2 and 3.)

The PTO relies on one reference to support its assertion that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The PTO cites Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) for support for the conclusion that not all genes with increased expression in cancer have a known or published role in cancer. Applicants respectfully submit that this reference does not

satisfy the PTO's burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not less-prevalent ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker. Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists.

Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease.

Applicants submit that a lack of known role for PRO1557 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1557 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors.

As further evidence that Hu is inapplicable to the utility of the claimed antibodies, Applicants submit as Exhibit 4, the publication by Wu *et al.* (Gene 311:105-110 (2003)), which was cited by the PTO in co-pending and co-owned application Serial No. 10/063,713. Wu *et al.* identify a gene, BNF-1, as a putative extracellular matrix protein over-expressed in breast, lung and colon tumors, which were the only tumors tested. Wu found that in 3 out of 11 breast tumor samples, BNF-1 was up-regulated about 2-fold to 3-fold. Wu at 107. Wu found that BNF-1 was up-regulated about 2-fold to 3-fold in 2 out of 6 lung tumor samples. *Id.* at 109. Wu found that BNF-1 was up-regulated about 2-fold to about 4-fold in 1 out of 6 colon tumor samples. *Id.* The coding region of BNF-1 is identical to the coding region of SEQ ID NO:81. Thus, Wu demonstrates that a gene identical to that of Applicants claims is over-expressed by 2-fold to 4-fold in some tumor samples, and Wu concludes that this gene is up-regulated in tumors. Wu further states that the expression pattern for BNF-1 is consistent with that of other solid tumor oncogenes. While Hu (presented by the PTO) merely indicates that less differentially expressed genes are less-often the subjects of scientific publications, Wu asserts that the 2-fold to 4-fold overexpressed BNF-1 gene is consistent with other solid tumor oncogenes. Thus, the teachings of Wu toward the utility of BNF-1, and similarly up-regulated oncogenes in general, are more applicable to the question of the utility of Applicants' claimed antibodies than the teachings of Hu. Accordingly, the evidence as a whole, supports Applicants' assertion of utility of the claimed antibodies.

As stated above, the standard for utility is not absolute certainty, but rather whether one of skill in the art would be more likely than not to believe the asserted utility. Hu is not sufficient to prove that a person of skill in the art would consider it unlikely that a gene differentially expressed in certain tumors can be used as a diagnostic tool since this reference does not teach against this. Moreover, Wu is contrary to the PTO's position, and supports Applicants' asserted utility of the claimed antibodies. Given the lack of support for the PTO's position, and the supporting evidence provided by Applicants for their position, one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly esophageal and kidney cancer.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1557 cDNA between esophageal tumor tissue and kidney tumor tissue, and normal esophageal tissue and normal kidney tissue, respectively. Therefore, it follows that expression levels of the PRO1557 gene can be used to distinguish esophageal tumor tissue from normal esophageal tissue and kidney tumor tissue from normal kidney tissue. The PTO has not offered any significant arguments or evidence to the contrary.

As explained below, it is more likely than not that the PRO1557 polypeptide is also differentially expressed in esophageal and kidney tumor tissue, such that the PRO 1557 polypeptide and antibodies that bind the PRO1557 polypeptide can be used to distinguish esophageal and kidney tumor from normal tissue. This provides utility for the claimed antibodies.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1557 polypeptide in esophageal tumor and kidney tumor, it is likely that the PRO1557 polypeptide is differentially expressed; and antibodies specific for proteins differentially expressed in certain tumors have utility as diagnostic tools.

The PTO states that even if the encoding nucleic acid had utility, the "encoded polypeptide has no such utility since there is no reason to suspect that there is alteration of polypeptide sequence or amount in esophageal or kidney tumor *versus* normal tissue." Office action at 3 (emphasis original). No substantiating evidence is presented. This statement in the Office Action does not satisfy the PTO's burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility. As stated above, the standard for establishing a use for a claimed invention is not absolute or even statistical certainty, and thus a *necessary* correlation between mRNA levels and protein levels is not required.

The PTO cites no evidence that would cast any doubt on the Applicants assertion that in general, there is a positive correlation between changes in mRNA level and changes in the encoded protein level.

In further support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants submit herewith a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 5). This declaration was submitted in connection with the related co-pending and co-owned application Serial No. 10/063,557. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also submit herewith a copy of the declaration of Paul Polakis, Ph.D. (attached as Exhibit 6), an expert in the field of cancer biology, originally submitted in a related and co-owned patent application Serial No. 10/032,996. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In

> fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (submitted herewith as Exhibit 7) and (4th ed. 2002) (submitted herewith as Exhibit 8)). Figure 9-2 of Exhibit 7 shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Exhibit 7 provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Exhibit 7 at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Exhibit 7 at 453 (emphasis added). Thus, as established in Exhibit 7, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Exhibit 8, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Exhibit 8 at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Exhibit 8 illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Exhibit 8 at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for

regulating protein expression, "[f]or most genes transcriptional controls are paramount." Exhibit 8 at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (submitted herewith as Exhibit 9) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, submitted herewith as Exhibit 10. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression." Exhibit 10 at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Exhibit 10 at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Exhibit 10 at 7.

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), submitted herewith as Exhibit 11, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Together, the declarations of Grimaldi and Polakis, the accompanying references, and the excerpts and references provided above all establish that the accepted understanding in the art is

that there is a reasonable correlation between changes in gene expression and the level of the encoded protein. In light of the lack of support for any argument by the PTO to the contrary, Applicants submit that they have established that it is more likely than not that one of skill in the art would believe that because the PRO1557 mRNA is expressed at a higher level in esophageal tumor and kidney tumor compared to normal esophageal and normal kidney tissue, respectively, the PRO1557 polypeptide will have the same expression pattern. This differential expression of PRO1557 and related polypeptides make antibodies specific for such polypeptides useful as diagnostic tools for cancer.

The Claimed Antibodies would have Diagnostic Utility even if there is no Direct Correlation between Gene Expression and Protein Expression

Even assuming *arguendo* that, there is no direct correlation between changes in gene expression and changes in protein expression for PRO1557, which Applicants submit is not true, an antibody to a polypeptide encoded by a gene that is differentially expressed in cancer would **still** have a credible, specific and substantial utility.

In paragraph 6 of the Grimaldi Declaration, Exhibit 5, Mr. Grimaldi explains that:

> However, even in the rare case where the protein expression does not correlate with the mRNA expression, this still provides significant information useful for cancer diagnosis and treatment. For example, if over- or under-expression of a gene product does not correlate with over- or under-expression of mRNA in certain tumor types but does so in others, then identification of both gene expression and protein expression enables more accurate tumor classification and hence better determination of suitable therapy.

This conclusion is echoed in the Declaration of Avi Ashkenazi, Ph.D. (attached as Exhibit 12), an expert in the field of cancer biology. This declaration was previously submitted in connection with co-pending application Serial No. 09/903,925. Applicants submit that simultaneous testing of gene expression and gene product expression enables more accurate tumor classification, even if there is no positive correlation between the two. This leads to better determination of a suitable therapy.

This is further supported by the teachings in the article by Hanna and Mornin (attached as Exhibit 13). The article teaches that the HER-2/neu gene has been shown to be amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the

amplification of the HER-2/neu gene (by FISH) as well as the overexpression of the HER-2/neu gene product (by IHC). Even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Applicants have established that it is the general, accepted understanding in the art that there is a positive correlation between changes in gene expression and changes in protein expression. However, even when this is not the case, an antibody to a polypeptide encoded by a gene that is differentially expressed in cancer would still have utility. Thus, Applicants have demonstrated another basis for supporting the asserted utility for the claimed antibodies.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

The PTO has not offered any arguments or cited any references to establish "that one of ordinary skill in the art would reasonably doubt" that the disclosed polypeptide is differentially expressed in certain tumors and that the claimed antibodies can be used as diagnostic tools. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly esophageal and kidney cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Antibodies

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed antibodies related to PRO1557. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1557 gene in certain types of cancer cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene encoding the PRO1557 polypeptide is expressed at least two-fold higher in esophageal tumor tissue and kidney tumor tissue compared to normal esophageal tissue and normal kidney tissue, respectively. These data are strong evidence that the PRO1557 gene and polypeptide are associated with esophageal and kidney tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1557 gene and polypeptide with two specific diseases. Use of the claimed antibodies a diagnostic tool for cancer, particularly esophageal tumor and kidney tumor, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

The PTO has asserted three arguments for why there is a lack of a substantial utility: (1) the data reporting that the PRO1557 gene is differentially expressed in certain tumors is not sufficient because there is not sufficient information regarding expression levels, and because the information is too sparse to allow the encoding polynucleotide to be used; (2) that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue; and, (3) that because there is no *necessary* correlation between gene amplification and protein expression, the claimed antibodies cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO1557 gene in esophageal tumor tissue and kidney tumor tissue compared to normal esophageal tissue and normal kidney tissue, respectively, are real and significant. This declaration also indicates that given the at least two-fold difference in expression levels, the disclosed nucleic acids, corresponding polypeptides and antibodies thereto, have utility as cancer diagnostic tools. Applicants have also shown that the precise level of expression and activity or role of the PRO1557 polypeptide in cancer is irrelevant. Resolution of these issues is not required to use the claimed antibodies as tumor diagnostic tools – one does not have to know why the PRO1557 polypeptide is differentially expressed in certain tumors to use it as a tumor marker.

Second, Applicants have shown that the Hu *et al.* reference cited by the PTO does not teach that genes differentially expressed in cancer cannot be used as diagnostic tools. In fact, Hu does not address this issue, either directly or indirectly, and therefore does offer no support for the PTO's position. In contrast, evidence submitted by Applicants, Wu *et al.*, does support Applicants' asserted utility based on the level of expression observed for the PRO1557 gene.

Applicants submit that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in the encoded protein levels. The PTO has not offered any substantial reasoning or evidence to the contrary. One of skill in the art will recognize that antibodies to polypeptides differentially expressed in certain cancers have utility as diagnostic tools for cancer.

Applicants have also presented the declarations of two experts in the field, along with supporting references, which establish that even in the anomalous case where there is no positive correlation between gene expression and expression of the encoded protein, the simultaneous monitoring of both is useful for diagnosis and further classification of the cancer.

Finally, the PTO asserts that there is no asserted specific utility. Applicants have pointed out that the substantial utilities described above are specific to the claimed antibodies because the PRO1557 gene and polypeptide are differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of antibodies.

Thus, given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as a diagnostic agent. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing some beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely . . . A commercially successful product is not required . . . Nor is it essential that the invention accomplish all its intended functions . . . or operate under all conditions . . . partial success being sufficient to demonstrate patentable utility . . . In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO1557 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO rejected Claims 1-6 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that because the claimed invention is not

supported by a substantial, specific and credible utility, the claims are not enabled. The PTO states that further experimentation would be required to use the claimed antibodies because the specification does not provide a definite function or disease association for the protein of SEQ ID NO:82.

Applicants respectfully traverse.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants therefore request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, based on a lack of utility.

Rejection under 35 U.S.C. §102(b) – Anticipation

The PTO has rejected Claims 1-6 as anticipated under 35 U.S.C. §102(b) by WO 00/70049. The PTO states that WO 00/70049 teaches a protein sequence that is 100% identical to Applicants' SEQ ID NO: 82, and antibodies specific thereto. As discussed above, the instant claimed subject matter has utility based upon the data in Example 18 and the instant application is a continuation of PCT/US00/23328; therefore, the present claims are entitled to the filing date of August 24, 2000. WO 00/70049 is not prior art under § 102(b).

WO 00/70049 was published on November 23, 2000, which is subsequent to the filing of priority application PCT/US00/23328 (August 24, 2000). Again, PCT/US00/23328 discloses the differential expression data which provides utility for the instant claims, and Applicants are entitled to the filing date of August 24, 2000. Therefore, WO 00/70049 cannot be cited under § 102(b).

In view of the above discussion, reconsideration and withdrawal of the rejection under § 102(b) is respectfully requested

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: April 11, 2005

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